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Reply to Ozaras et al

TO THE EDITOR—We appreciate the concern raised by Ozaras et al regarding the hepatitis B surface antibody (anti-HBs) status of the 103 hepatitis C virus (HCV)–infected patients who were hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (anti-HBc) positive and had no evidence of hepatitis B virus (HBV) reactivation during or following treatment with ledipasvir/sofosbuvir [1, 2]. To address this concern, we retrospectively determined the anti-HBs status of the 103 patients who were positive for anti-HBc, by analyzing archived samples using the ADVIA Centaur Anti-HBs Reagent Kit (Seimens Healthcare Diagnostics, Tarrytown, New York). Of 103 patient samples analyzed, 37 (36%) were anti-HBs negative, 63 (61%) were anti-HBs positive, and 3 (3%) could not be evaluated because the remaining samples were inadequate. Of the 2 patients identified in our initial analysis as being HBsAg negative and anti-HBc positive with detectable HBV DNA below the lower limit of quantification, both were found to be negative for anti-HBs. Importantly, none of the 37 anti-HBc–positive/HBs-negative patients experienced HBV reactivation in our study, including the 2 patients with detectable HBV DNA.

Published case reports suggest that clinical HBV reactivation is a rare occurrence. The majority of described cases occurred in persons who were HBsAg positive, indicative of active HBV infection. Some of these patients may have met criteria for HBV treatment prior to the initiation of HCV therapy. In the case series reported by Bersoff-Matcha and colleagues from the US Food and Drug Administration, the status of HBV infection was incomplete for many patients, which limits the interpretation of the risk of HBV flare, particularly among those reported to be HBsAg negative [3]. Liu

and colleagues presented data in 2016 on HBV reactivation in 134 patients receiving DAA treatment for HCV [4]. Of the 134 patients, 81 patients were HBsAg negative and anti-HBc positive. No evidence of HBV reactivation was observed in these 81 patients, which is consistent with our findings. The precise risk of HBV reactivation is difficult to estimate, but the relatively high global prevalence of HBV infection in persons with chronic HCV infection and the small number of cases of HBV reactivation or alanine aminotransferase flare reported among the >1 million persons treated with direct-acting antivirals (DAAs) for HCV suggest that the risk is low [5].

We believe that HCV-infected patients should be screened for HBV infection prior to initiation of DAAs and, for those found to have active HBV infection, HBV treatment guidelines should be followed. Given the benefits of successful HCV treatment, the risk of HBV reactivation should not be overstated.

Notes

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Time Efficiency Assessment of Antimicrobial Stewardship Strategies

TO THE EDITOR—We read with interest the recent article in *Clinical Infectious Diseases* by Tamma et al [1], which focused on the efficacy of different antimicrobial stewardship methods, demonstrating that post-prescription review with feedback (PPRF) was more effective at reducing antimicrobial consumption over time than pre-prescription authorization. The study was performed on medical inpatients, but hospitals contain many other cohorts, such as surgical inpatients, in whom antimicrobial use is also high and often inappropriate [2]. PPRF can take many forms but is invariably both human resource and time intensive. Many hospitals may lack the resources to initiate this level of stewardship universally [3, 4], and there is therefore a need to identify the

Table 1. Number, Proportion and Rate of Interventions by Stewardship Modality

Stewardship Approach	Prescriptions Reviewed, No.	Stewardship Interventions		Intervention Rate, Interventions per Hour of Stewardship (95% CI)	Hazard Ratio (95% CI)
		No. (10)	Odds Ratio (95% CI)		
Telephone	691	30 (4.34)	...	0.48 (.34–.69)	...
Medical round	802	75 (9.35)	2.27 (1.46–3.52)	2.26 (1.8–2.83)	4.69 (3.07–7.17)
Surgical round	435	162 (37.24)	13.07 (8.64–19.79)	1.70 (1.36–1.98)	3.53 (2.39–5.21)

Abbreviation: CI, confidence interval.

form of PPRF that most efficiently impacts inappropriate antimicrobial prescribing [5, 6].

We performed a prospective, observational study that compared different forms of PPRF: ward round reviews on acute medical wards, ward round reviews on surgical recovery wards, and telephone reviews with clinical teams caring for patients receiving carbapenems, cephalosporines, or quinolones. Each stewardship review episode was performed by 2 microbiologists and a pharmacist, who collected no more data than needed for routine practice and were not aware that the data would be used comparatively in the study. The 3 stewardship modalities occurred daily for 45, 90, or 60 minutes—for medical rounds, surgical rounds, and telephone reviews, respectively—and there was no overlap in the patients reviewed. All antimicrobial prescriptions reviewed were quantified and any intervention was recorded, with an intervention defined as a change to antimicrobial prescription, including starting or stopping treatment with a medication or modifying the duration of treatment or mode of administration. For the purpose of comparison, we considered telephone stewardship to be the control group. We calculated both the proportion of reviews resulting in an intervention and the rate of intervention per hour of stewardship across the 3 stewardship modalities.

A total of 1928 antimicrobial prescriptions were reviewed. Both surgical (37.24%) and medical (9.35%) stewardship ward rounds resulted in a significantly higher proportion of interventions than telephone reviews (4.34%) (Table 1). However, after

controlling for time, the rate of interventions per hour was higher for medical stewardship rounds (2.26 interventions / hour) than for both surgical (1.70 interventions / hour) and telephone (0.48 interventions / hour) rounds (Table 1).

In conclusion, our study supports the observations made by Tamma et al [1] that hospital ward-based PPRF, though resource intensive, is an effective form of antimicrobial stewardship. We extend their findings by raising the importance of time efficiency, demonstrating that although surgical patient stewardship rounds result in a high absolute number and proportion of interventions, they are labor intensive, and medical ward rounds resulted in a similar number of interventions per hour of stewardship time. Both approaches were significantly better than telephone stewardship in terms of both the proportion and rate of stewardship interventions. We propose that other hospitals looking to assess and prioritize the impact of their stewardship programs should also incorporate a standardized time-based measure of stewardship efficiency.

Notes

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Optimizing Proton Pump Inhibitor Use to Reduce Antimicrobial Resistance Rates?

TO THE EDITOR—With the greatest interest we read the study of Huizinga and colleagues on the impact of proton pump inhibitor (PPI) use on colonization with extended-spectrum β -lactamase-producing Enterobacteriaceae [1]. In our multicenter Antibiotic Therapy Optimization Study (ATHOS), the study group obtained rectal swabs of 4376 patients on hospital admission and determined the prevalence for